Funcitonalization of B/C-ring of Daphnane and Tigliane Diterpenes by Wender's Group

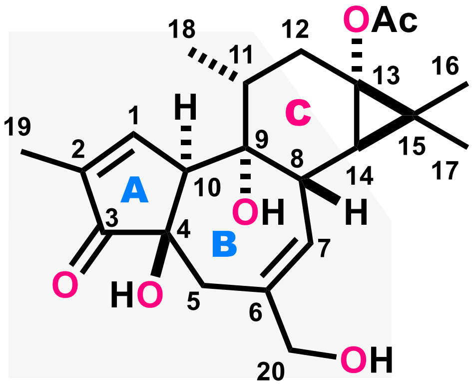
2022/07/09 Ayumu Watanabe

Contents

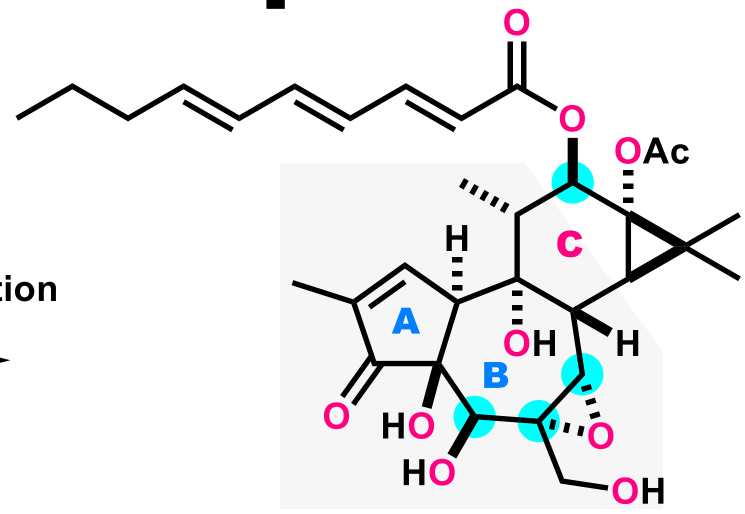
Contents

Daphnane Tigliane Diterpenes

tigliane

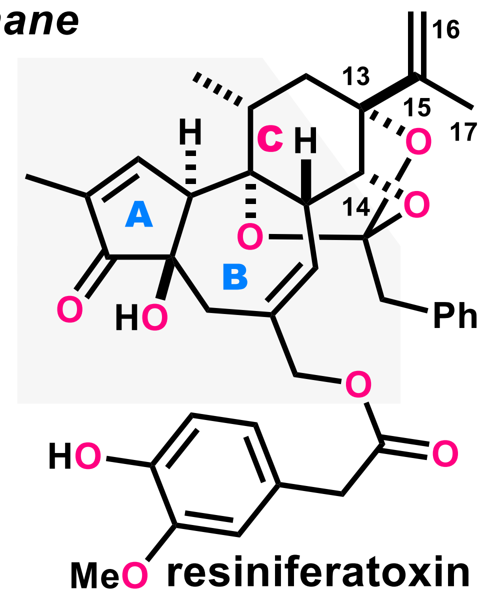


C5, 6, 7, 12 oxidation

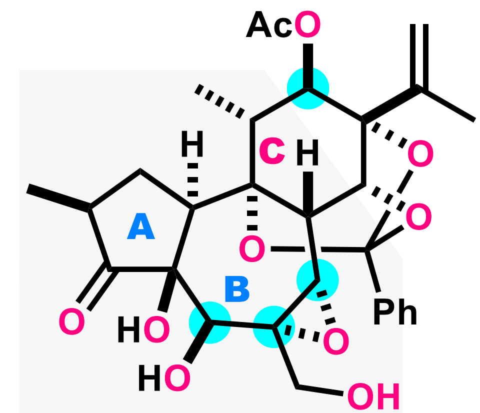


prostratin (2 examples) **acerifolin A (not reported)**

daphnane



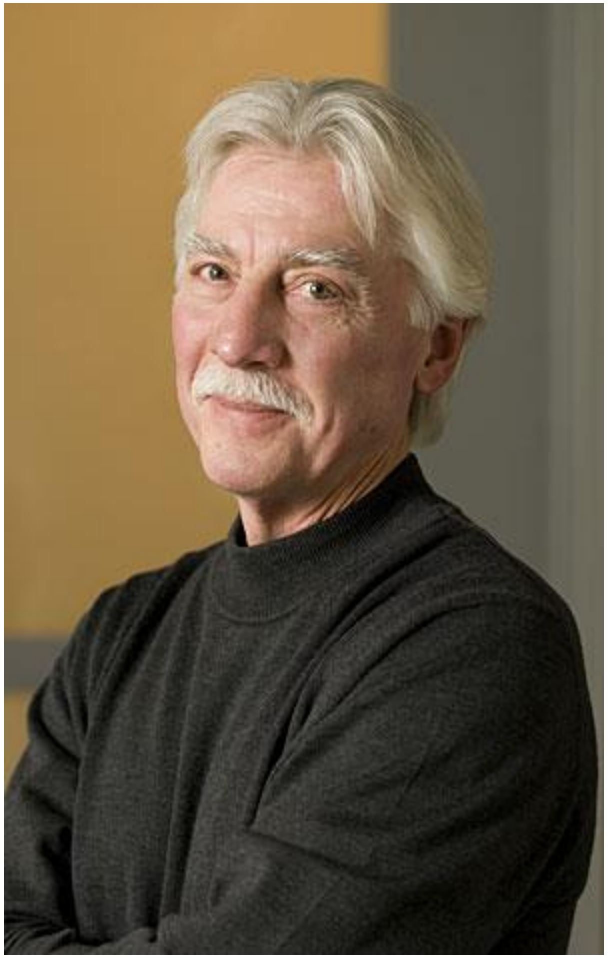
C5, 6, 7, 12 oxidation



MeO resiniferatoxin (4 examples) **yuanhuapin (not reported)**

Tong, G.; Liu, Z.; Li, P., *Chem* **2018**, *4*, 2944. Hirose, A.; Watanabe, A.; Ogino, K.; Nagatomo, M.; Inoue, M., *J. Am. Chem. Soc.* **2021**, *143*, 12387. Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y., *J. Am. Chem. Soc.* **1997**, *119*, 12976. Hashimoto, S.; Katoh, S.; Kato, T.; Urabe, D.; Inoue, M., *J. Am. Chem. Soc.* **2017**, *139*, 16420. Hikone, Y.; Kato, T.; Nagatomo, M.; Inoue, M., *Org. Lett.* **2022**, *24*, 929.

Prof. Paul A. Wender

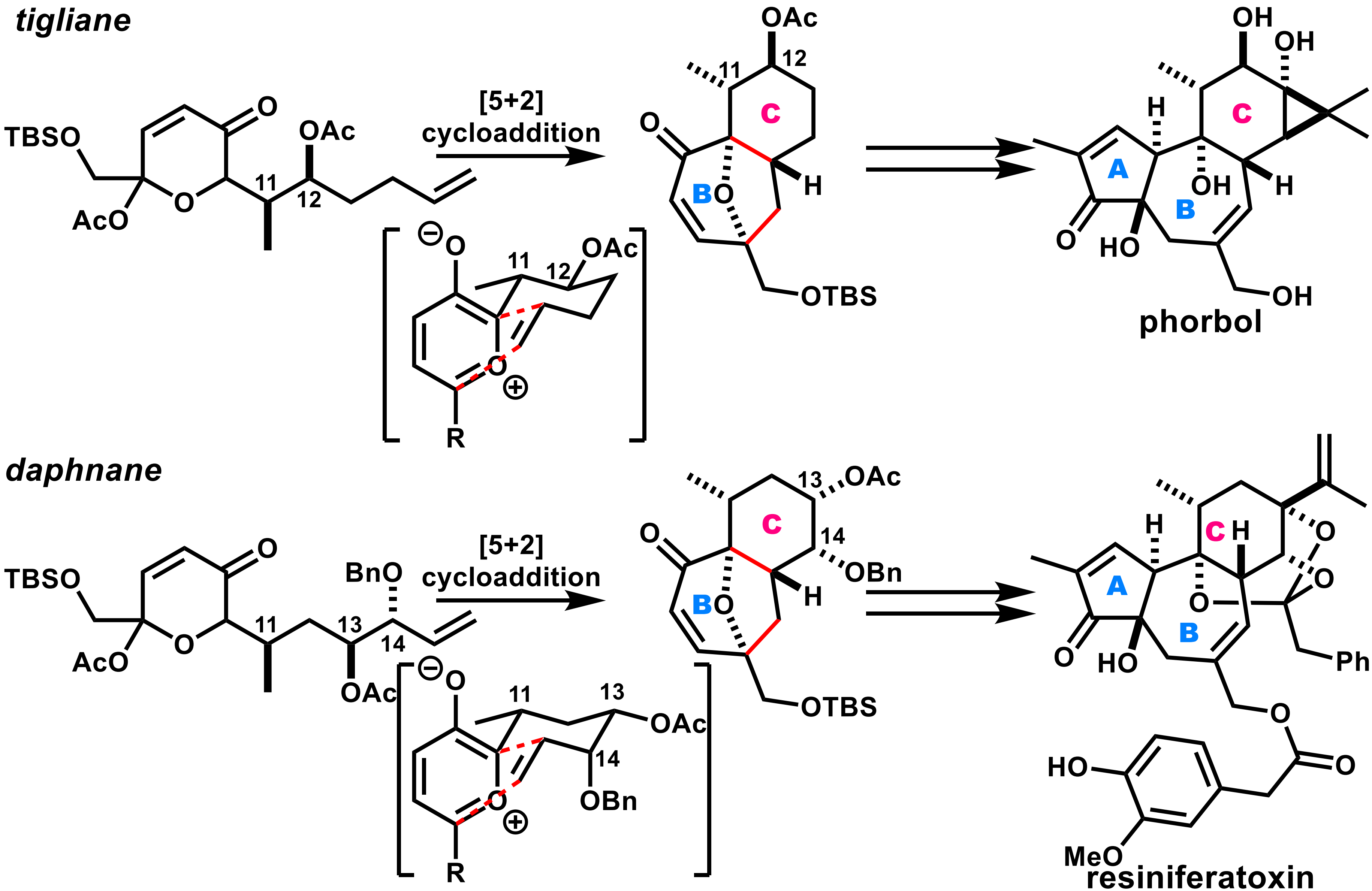


1969	B.S. @ Wilkes College
1973	Ph.D @ Yale University
	(Prof. Frederick E. Ziegler)
1974-	NIH Postdoctral fellow
	@ Columbia University
1974-	Assistant Professor
	@ Harvard University
	Associate Professor
	@ Harvard University
1982-	Professor of Chemistry
	@ Stanford University

Research: Organic synthesis (Function-Oriented-Synthesis)
Catalysis, Chemical biology

Example of total synthesis: taxol, phorbol, resiniferatoin,
prostratin, bryostatin

B/C- ring construction by Wender

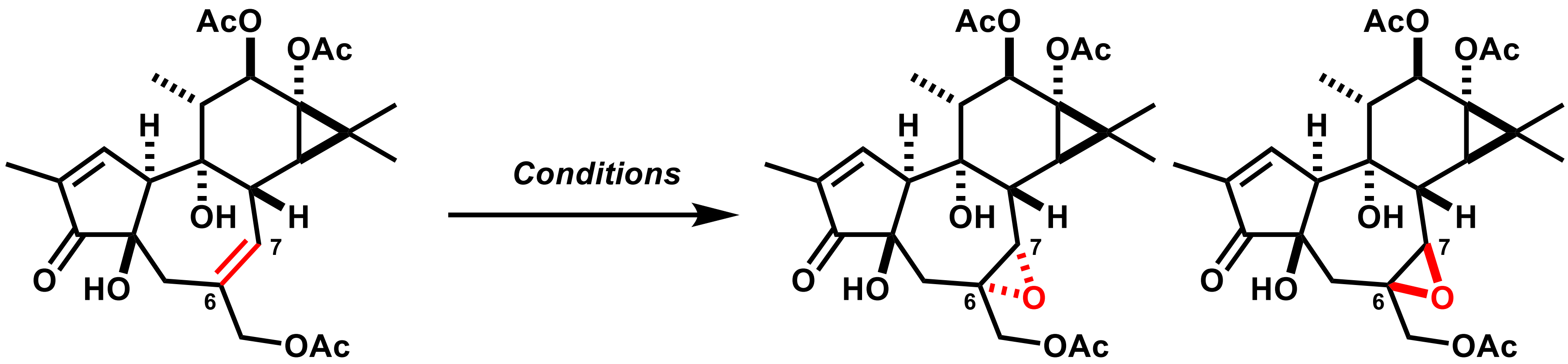


Wender, P. A.; Rice, K. D.; Schnute, M. E., *J. Am. Chem. Soc.* **1997**, *119*, 7897.
Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y., *J. Am. Chem. Soc.* **1997**, *119*, 12976.

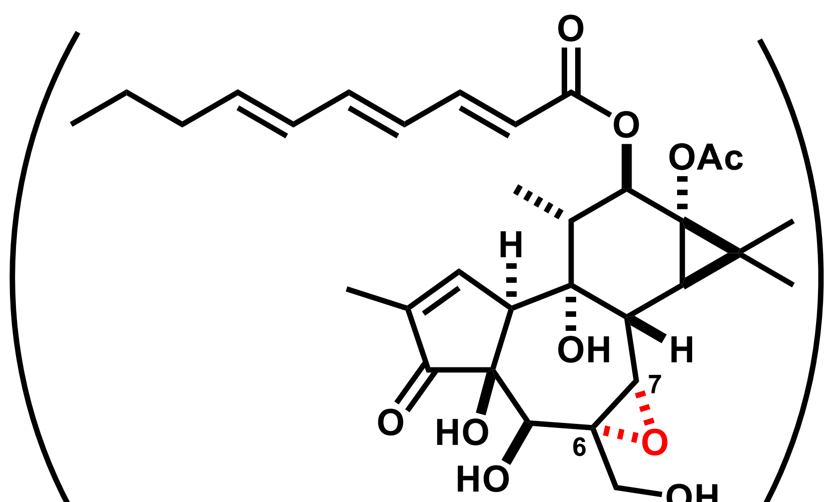
Contents

Epoxidation of B-ring 1

Intrinsic facial selectivity for direct epoxidation



phorbol triacetate **desired** **undesired**

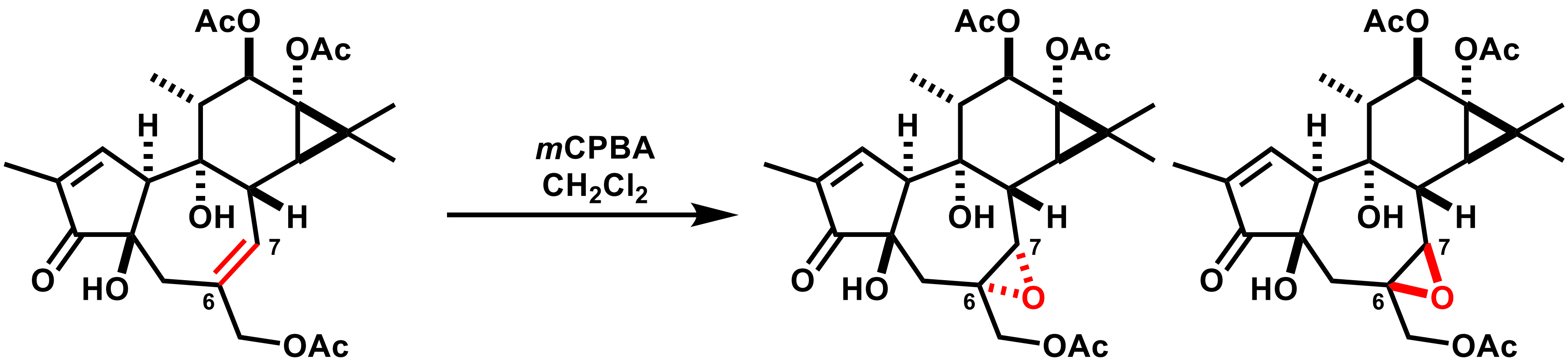


acerifolin A

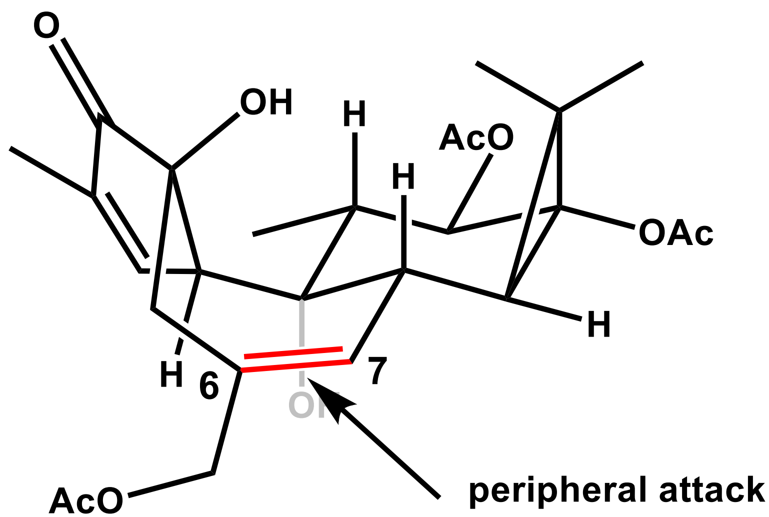
1) Hecker, E.; Schmidt, R., *Prog. Chem. Org. Nat. Prod.* **1974**, *31*, 377.

Epoxidation of B-ring 2

Intrinsic facial selectivity for direct epoxidation

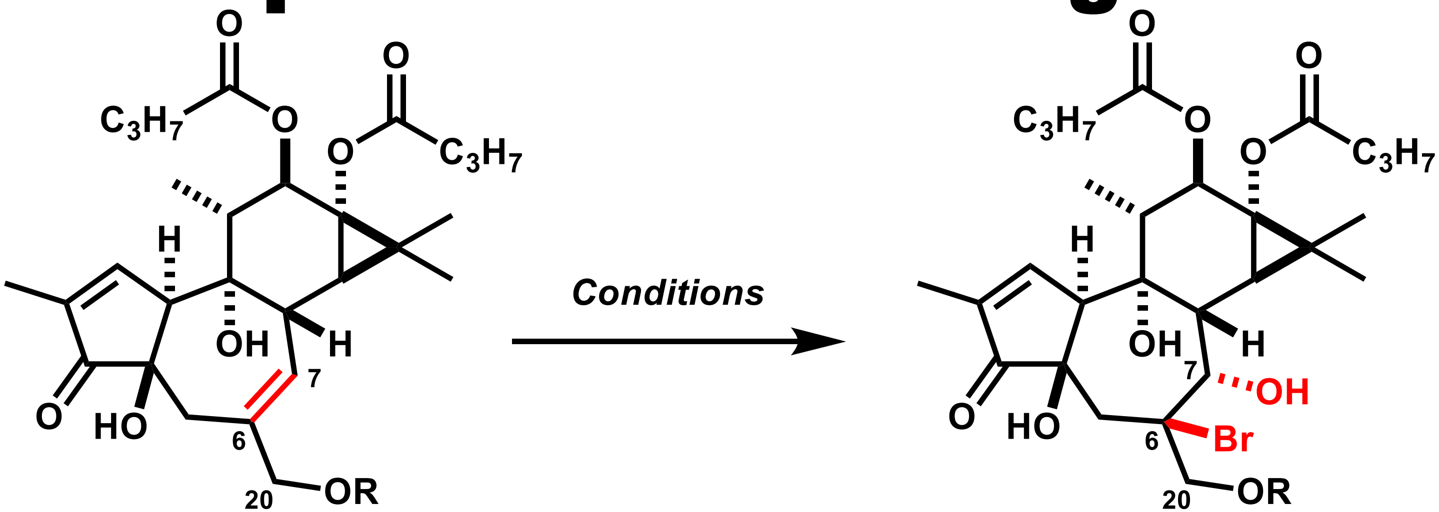


phorbol triacetate **not obtained** **obtained**



1) Hecker, E.; Schmidt, R., *Prog. Chem. Org. Nat. Prod.* **1974**, *31*, 377.

Epoxidation of B-ring 3



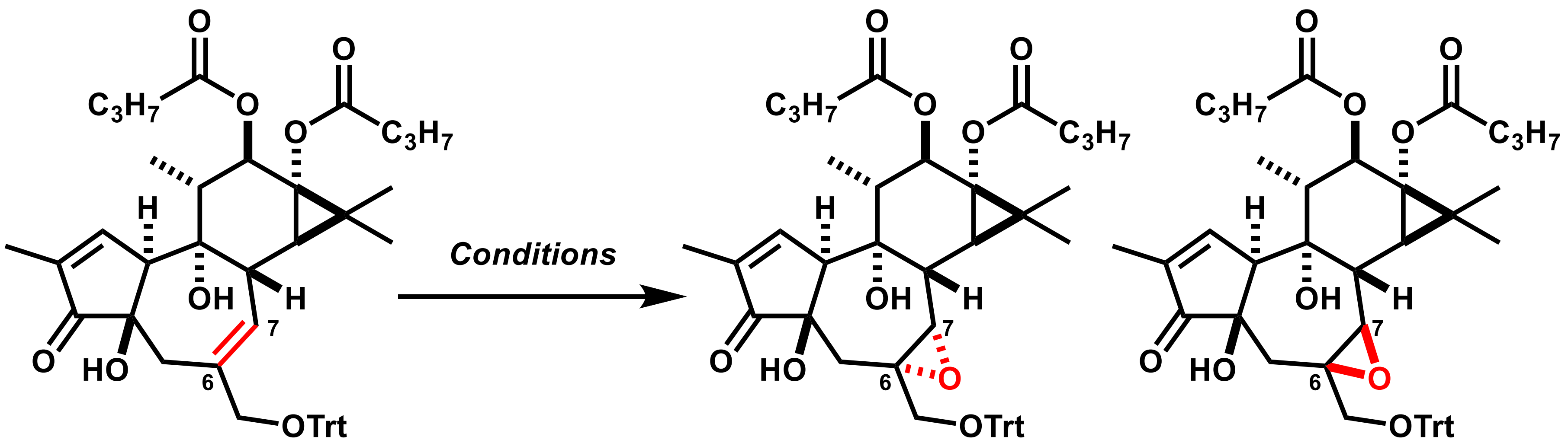
phorbol 12,13-dibhtyrate (PDBu)

Halohydrin formation attempts from phorbol 12,13-dibhtyrate (PDBu)   *NBA: N-bromoacetamide

entry	R	*Conditions*	Results
1	H	NBS (1.3 eq), acetone/H_2O, rt	Mixture, C20 aldehyde
2	COC_3H_7	NBS (1.1 eq), DME/H_2O (16/1), 0 ℃ to rt	No reaction
3	COC_3H_7	NBA, $HClO_4$ (cat.), dioxane/H_2O, 50 ℃ [2)]	Mixture, C20 aldehyde
4	TBDPS	NBS (1.1 eq), THF/H_2O, 0 ℃	C20 aldehyde
5	TBDPS	NBS (1.1 eq), NaOAc THF/H_2O, rt	No reaction
6	TBDPS	NBS (4.0 eq), NaOAc THF/H_2O, rt	Dibrominated

1) Boudreault, P.-L.; Mattler, J. K.; Wender, P. A., *Tetrahedron Lett.* **2015**, *56*, 3423.
2) Rodriguez, J.; Dulcere, J. P., *Synthesis* **1993**, *12*, 1177.

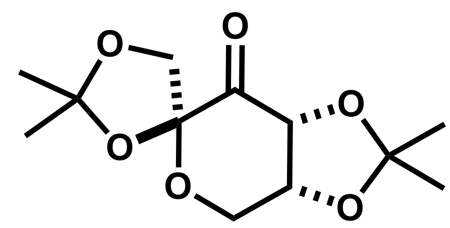
Epoxidation of B-ring 4



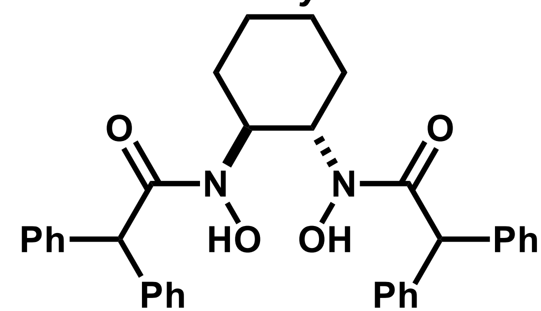
PDBu α-epoxide (desired) β-epoxide (undesired)

Enantioselective epoxidation from phorbol 12,13-dibhtyrate (PDBu)

entry	*Conditions* (equivalent)	Results
1	*Shi Catalyst A,* Oxone, K_2CO_3	β-epoxide
2	*Shi Catalyst ent-A,* Oxone, K_2CO_3	No reaction
3	Ti(O*i*-Pr)$_4$ (10), (+)-DIPT (12), TBHP (2)	α:β = 1:1.5
4	VO(acac)$_2$, *Ligand A*, aq. TBHP, CH_2Cl_2	80% (α:β = 1:1)[2]



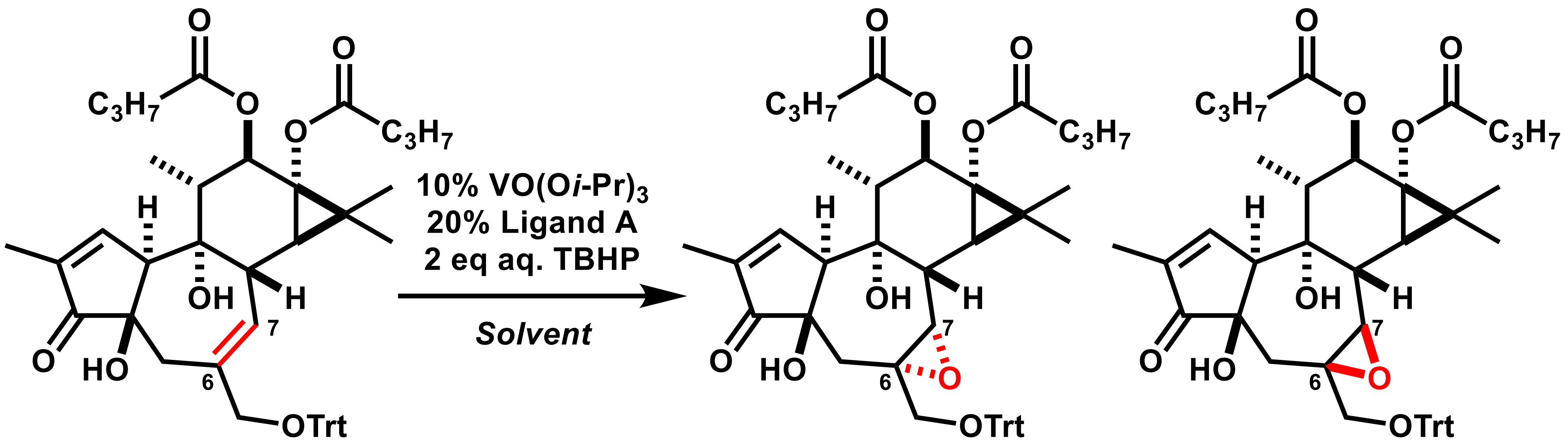
Shi Catalyst A



Ligand A

1) Boudreault, P.-L.; Mattler, J. K.; Wender, P. A., *Tetrahedron Lett.* **2015**, *56*, 3423.
2) Zhang, W.; Basak, A.; Kosugi, Y.; Hoshino, Y.; Yamamoto, H., *Angew. Chem., Int. Ed.* **2005**, *44*, 4389.

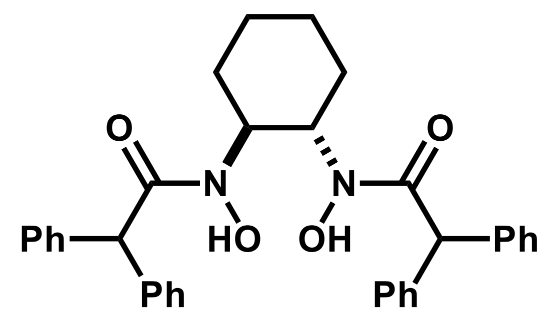
Epoxidation of B-ring 5



PDBu α-epoxide (desired) β-epoxide (undesired)

Solvent effect on epoxidation with PDBu and ligand A

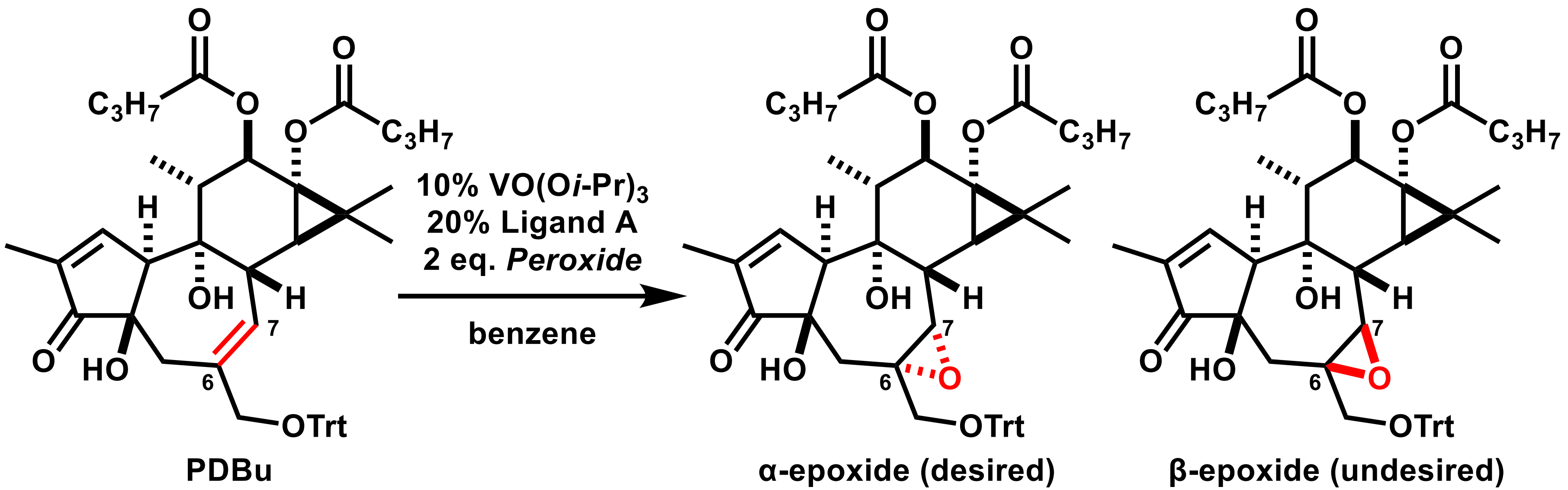
entry	*Solvent*	*Time* (h)	*Conversion* (%)	Results (α:β)
1	CH_2Cl_2	24	100	81% (1:1)
2	PhMe	24	100	84% (1:1)
3	benzene	12	100	84% (55:45)
4	acetone	24	48	44% (22:78)
5	THF	24	65	62% (β major)
6	$CHCl_3$	24	91	81% (1:1)



Ligand A

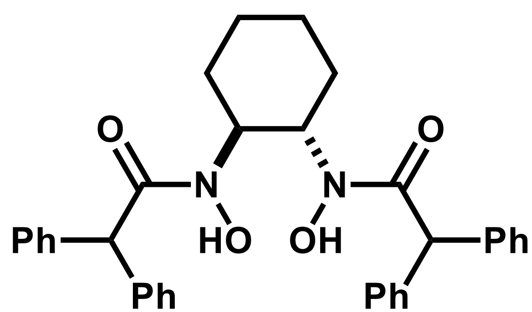
1) Boudreault, P.-L.; Mattler, J. K.; Wender, P. A., *Tetrahedron Lett.* **2015**, *56*, 3423.
2) Zhang, W.; Basak, A.; Kosugi, Y.; Hoshino, Y.; Yamamoto, H., *Angew. Chem., Int. Ed.* **2005**, *44*, 4389.

Epoxidation of B-ring 6



Peroxide effect on epoxidation with PDBu and ligand A

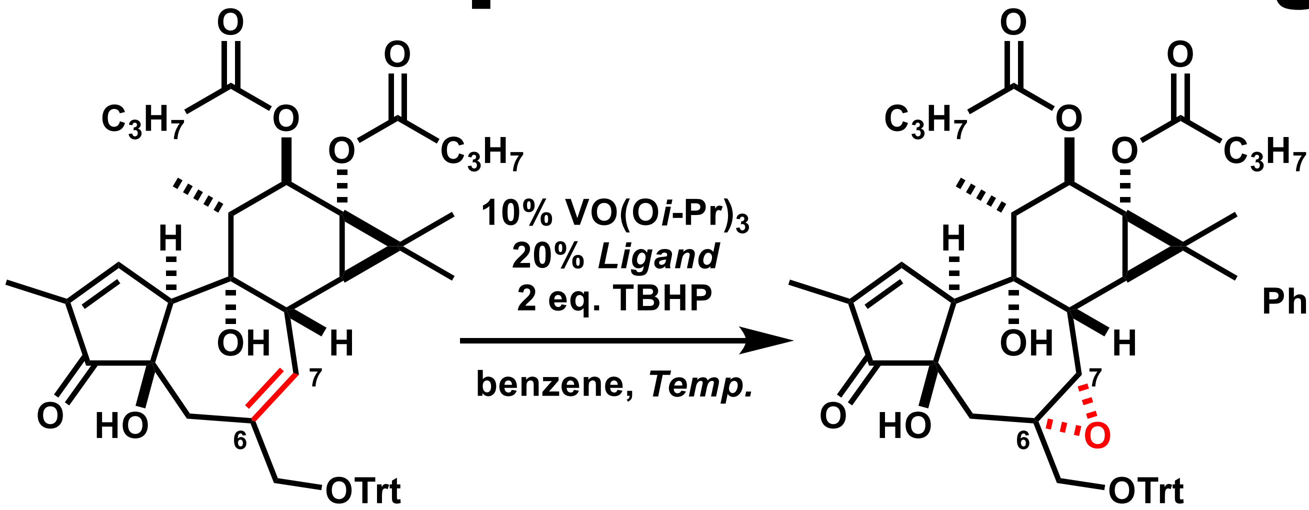
entry	*Peroxide*	*Time* (h)	*Conversion* (%)	Results (α:β)
1	aq. TBHP	24	100	84% (55:45)
2	TBHP (in decane)	24	100	79% (60:40)
3	Cumene hydroperoxide	48	80	82% (55:45)



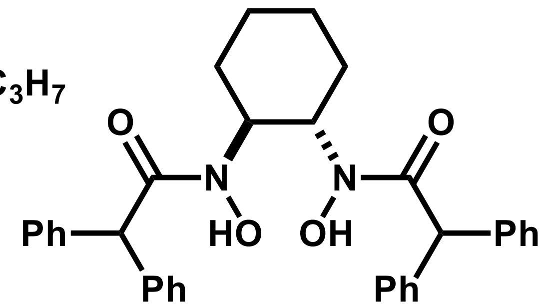
Ligand A

1) Boudreault, P.-L.; Mattler, J. K.; Wender, P. A., *Tetrahedron Lett.* **2015**, *56*, 3423.
2) Zhang, W.; Basak, A.; Kosugi, Y.; Hoshino, Y.; Yamamoto, H., *Angew. Chem., Int. Ed.* **2005**, *44*, 4389.

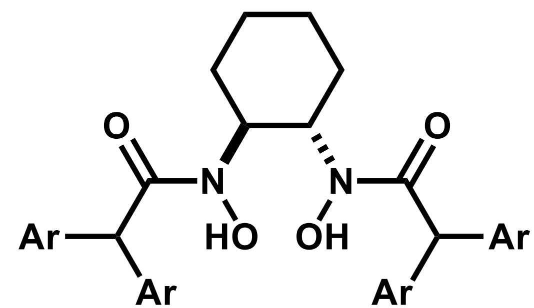
Epoxidation of B-ring 7



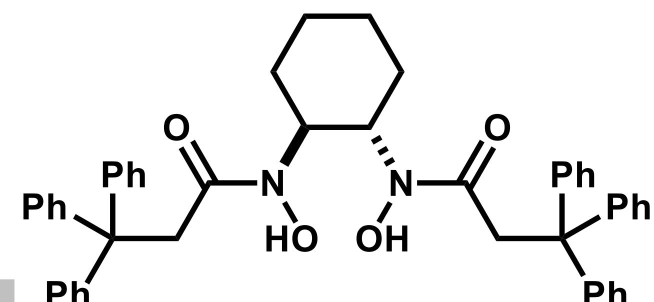
PDBu → α-epoxide (desired)



Ligand A



Ligand B
Ar = 3,5-Me$_2$Ph



Ligand C

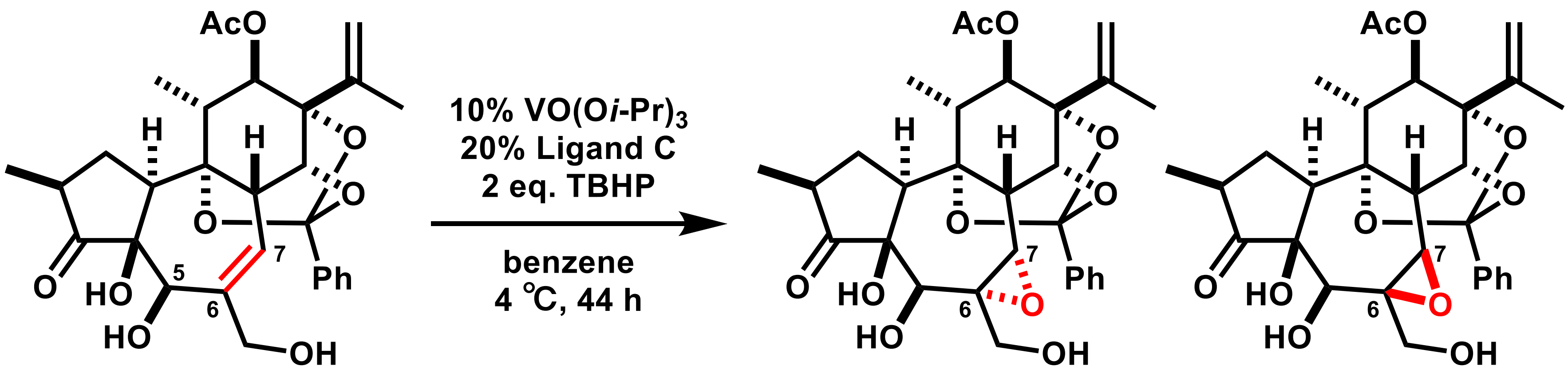
Ligand effect on epoxidation with PDBu and ligand A

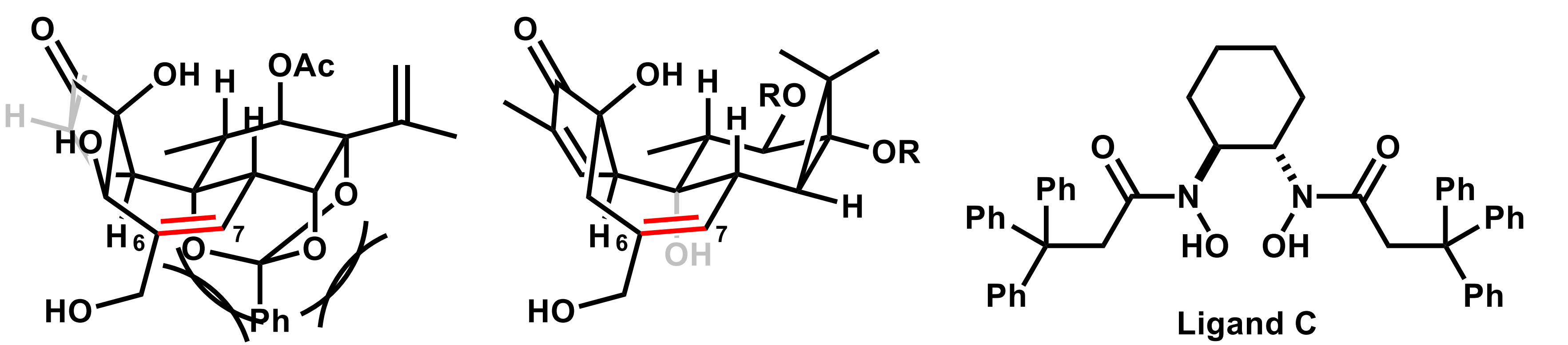
entry	*Ligand*	*Temp.*	*Time* (h)	Results (α:β)
1	A	0 ℃ to rt	12	84% (60:40)
2	A	4 ℃	96	78% (63:37)
3	B	0 ℃ to rt	36-48	85% (75:25)
4	B	4 ℃	120	73% (79:19)
5	C	0 ℃ to rt	>12	85% (80:20)
6	C	4 ℃	24	85% (89:11)

1) Boudreault, P.-L.; Mattler, J. K.; Wender, P. A., *Tetrahedron Lett.* **2015**, *56*, 3423.
2) Zhang, W.; Basak, A.; Kosugi, Y.; Hoshino, Y.; Yamamoto, H., *Angew. Chem., Int. Ed.* **2005**, *44*, 4389.

Epoxidation of B-ring 8

Application to daphnane diterpenes





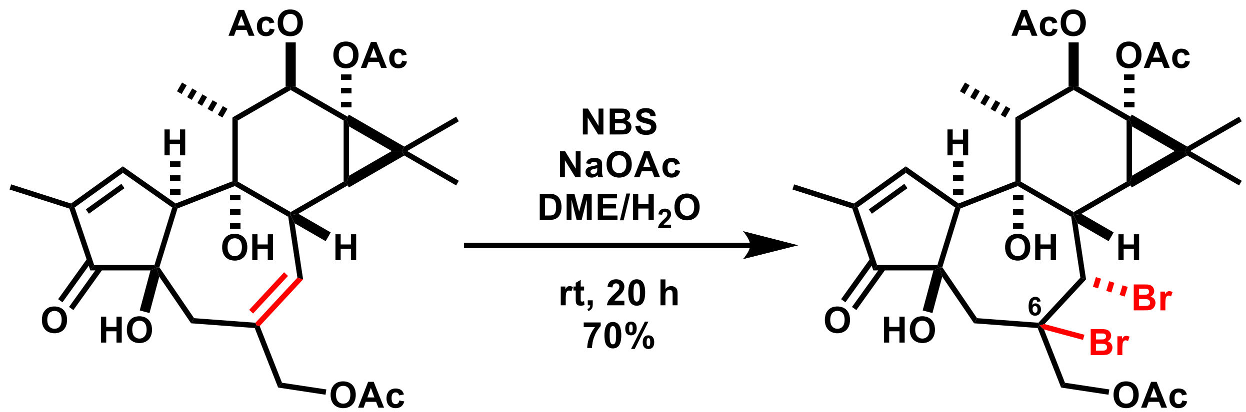
Wender's group says:
"Evidence suggests that the C5 alcohol and/or the oxidation of the A-ring play important roles in determining the stereochemical outcome of the epoxidation of des-epoxy-yuanhuapin."
In addition, daphnane's α-face is more hidered by bulky orthoester group than that of tigliane

---

1) Wender, P. A.; Buschmann, N.; Cardin, N. B.; Jones, L. R.; Kan, C.; Kee, J.-M.; Kowalski, J. A.; Longcore, K. E. *Nat. Chem.* **2011**, *3*, 615.

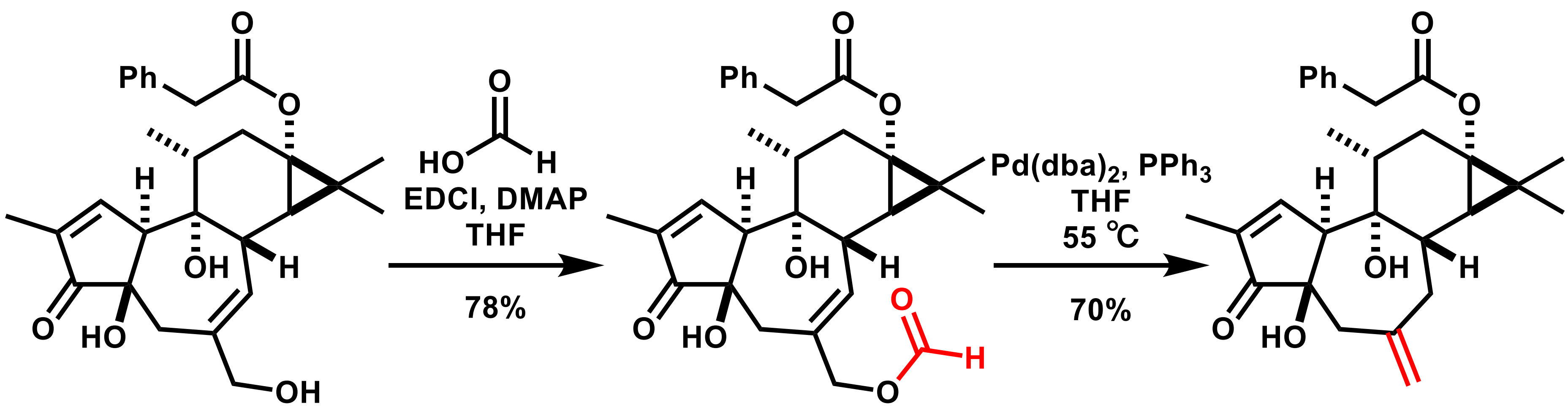
Other reactions of B-ring

Dibromination of B-ring (olefin protection)



The use of NaOAc was found to be essential for efficient dibromide formation.
Unambiguous stereochemical assignment of C6 by NMR spectroscopy was not possible.

Exo-olefin formation (<u>PATENT</u>)



1) Wender, P. A.; Kirschberg, T. A.; Williams, P. D., Bastiaans, H. M. M., Irie, K., *Org. Lett.* **1999**, *1*, 1009.
2) Wender, P. A., et al., US 2011/0014699 A1.

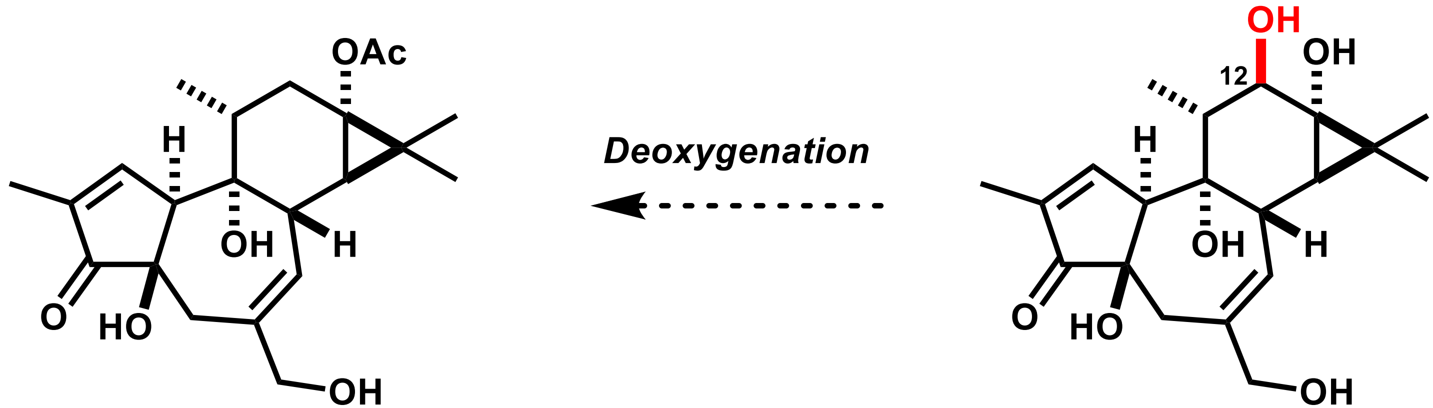
Contents

1. Introduction

2. B-ring functionalization
(oxidation, dibromination, exo-olefination)

3. C-ring functionalization
(phorbol to prostratin, prostratin analogs
tigliane to daphnane)

Phorbol and prostratin



prostratin
Activity: anti-HIV activity
(especially inducing latent HIV)
Isolation: *Homalanthus nutans*
(0.2 to 52 μg/g by weight from the tree stem)

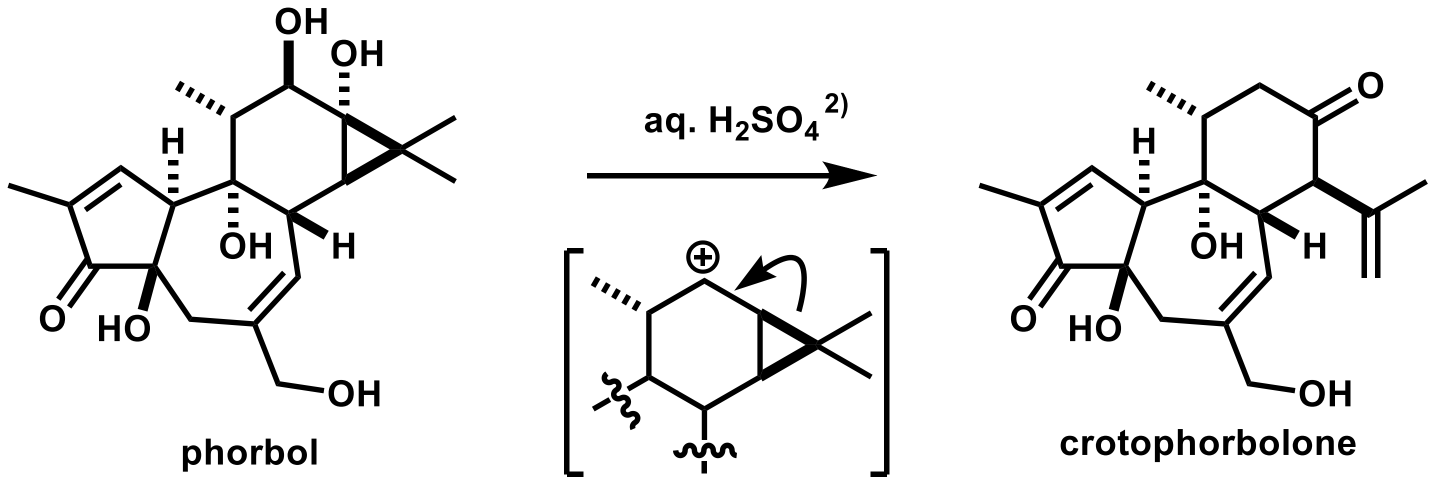
phorbol
Activity of its ester: tumor promoter

Isolation: *croton tiglinum*
(1.1-1.6% from croton oil)
croton oil: 1250 mL = 220 $

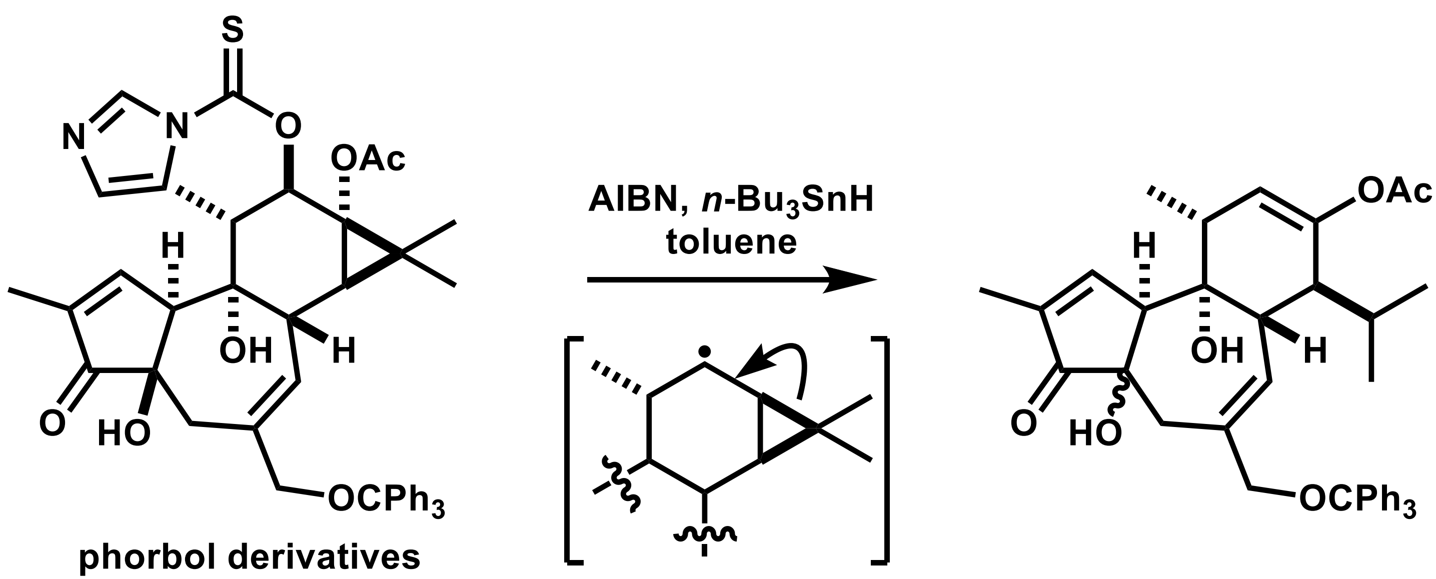
1) Wender, P. A., Kee, J.-M.; Warrington, J. M.; *Science* **2008**, *320*, 649.

Direct Deoxygenation of Phorbol

Acidic conditions



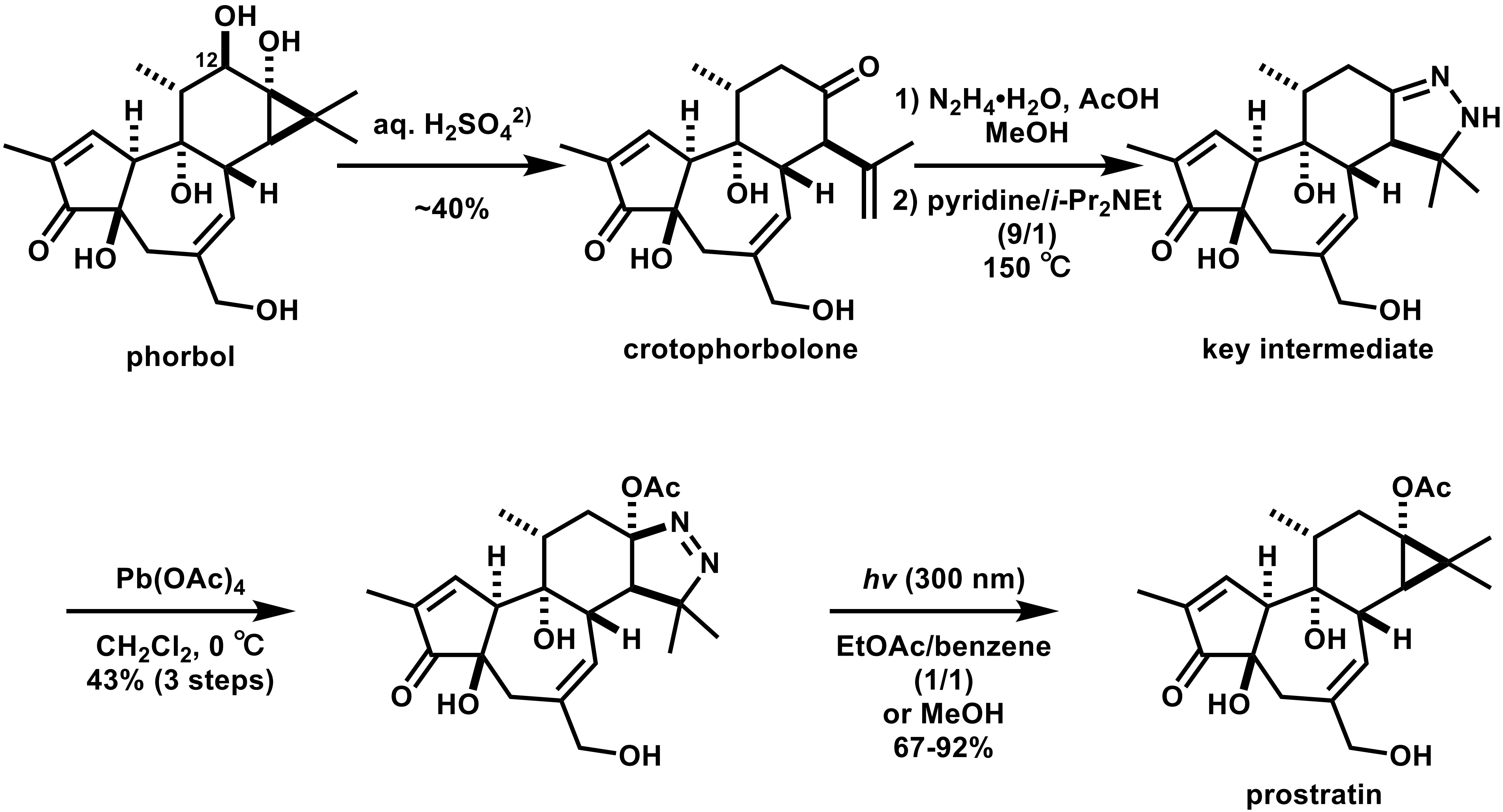
Radical conditions



Anionic conditions were not reported.

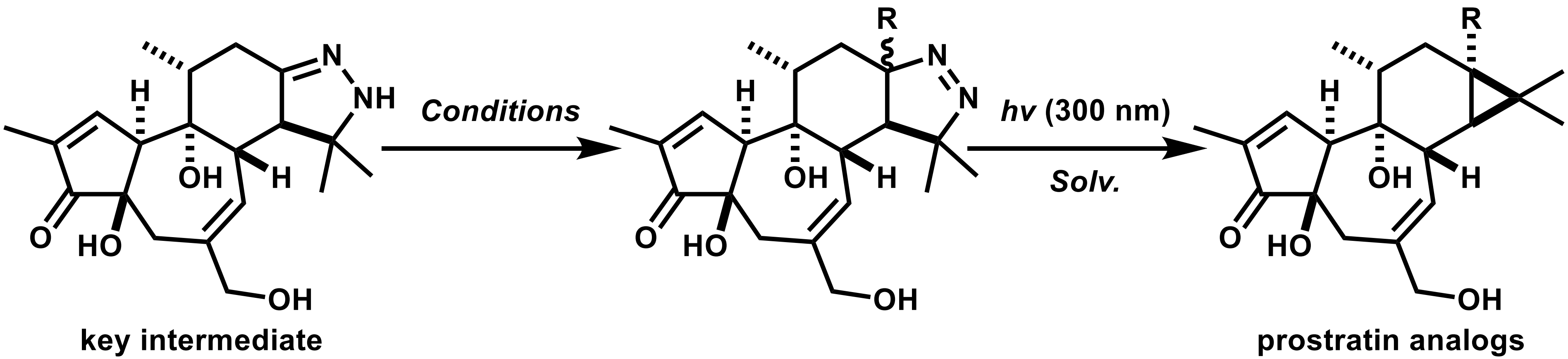
1) Wender, P. A., Kee, J.-M.; Warrington, J. M.; *Science* **2008**, *320*, 649.
2) Thielmann, H. W.; Hecker, E., *Liebigs Ann. Chem.,* **1969**, *728*, 158.

Synthesis of Prostratin from Phorbol



1) Wender, P. A., Kee, J.-M.; Warrington, J. M.; *Science* **2008**, *320*, 649.
2) Thielmann, H. W.; Hecker, E., *Liebigs Ann. Chem.,* **1969**, *728*, 158.

Synthesis of Prostratin Analogs 1



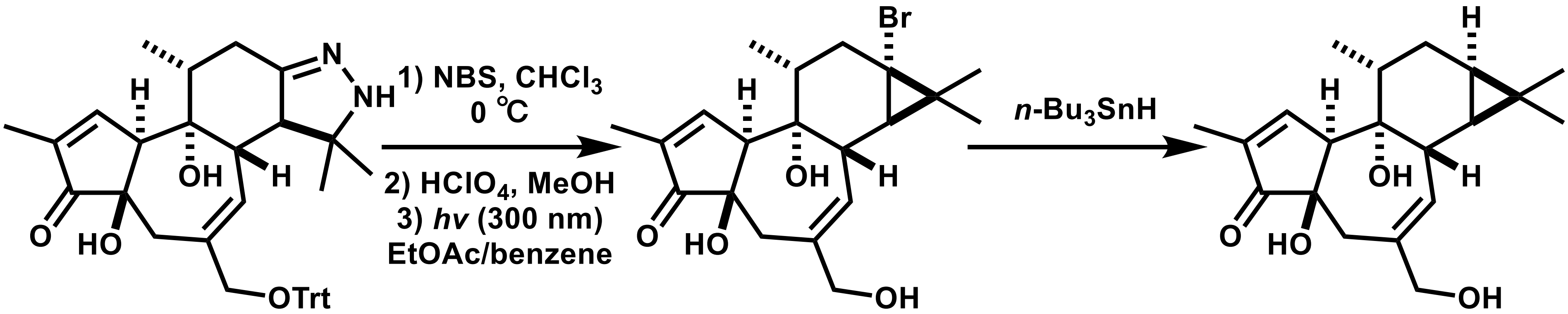
R	Conditions	Solv.	Yield*
AcO	$Pb(OAc)_4$, CH_2Cl_2	EtOAc/benzene or MeOH	29%
$PhCH_2COO$	$Pb(OAc)_4$, $PhCH_2COOH$ (50 eq), CH_2Cl_2	EtOAc/benzene or MeOH	32%
EtO	$PhI(OAc)_2$, EtOH	EtOAc	17%
$PhCH_2CH_2O$	$PhI(OAc)_2$, $PhCH_2CH_2OH$	EtOAc	16%

*4-step yield from crotophorbolone

1) Wender, P. A., Kee, J.-M.; Warrington, J. M.; *Science* **2008**, *320*, 649.

Synthesis of Prostratin Analogs 2

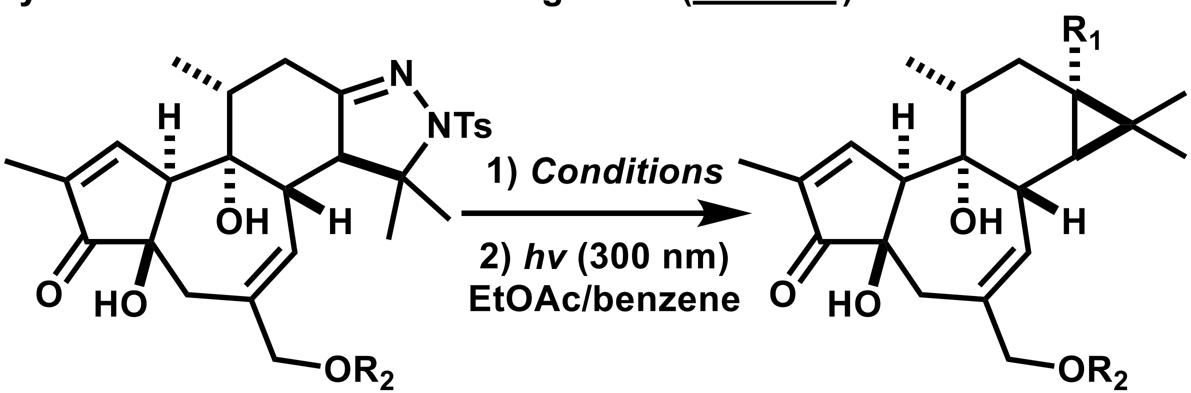
Synthesis of 12, 13-dideoxy tiglianes (PATENT)



key intermediate — 13-bromo tiglianes — 12, 13-dideoxy tiglianes

Yield is not mentioned, and "The usual analysis of the product confirms that the desired product XX is present" for all reactions

Synthesis of C13-substituted tiglianes (PATENT)



Ts intermediate using H_2NNHTs — 13-bromo tiglianes

R_1	Conditions
alkyl	$(alkyl)_3Al$
RNH, RCONH	RN^-, $RCON^-$
RS, RSe, CN	RS^-, RSe^-, CN^-

Experimental procedures were not present

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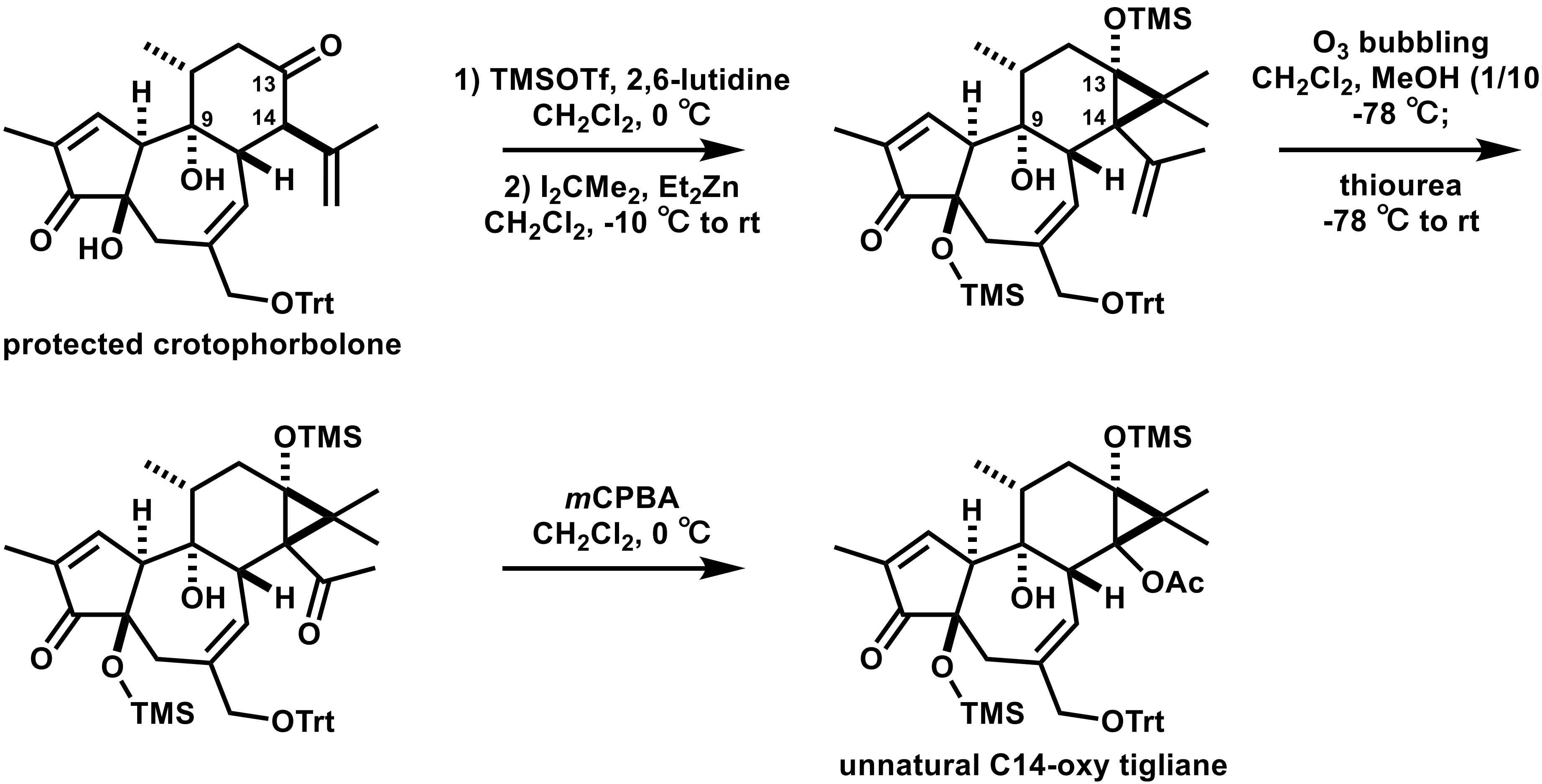
1) Wender, P. A., et al., US 2009/0187046 A1.

Synthesis of Unnatural C14-Oxy Tigliane

Synthesis of unnatural C14-oxy tigliane (<u>PATENT</u>)

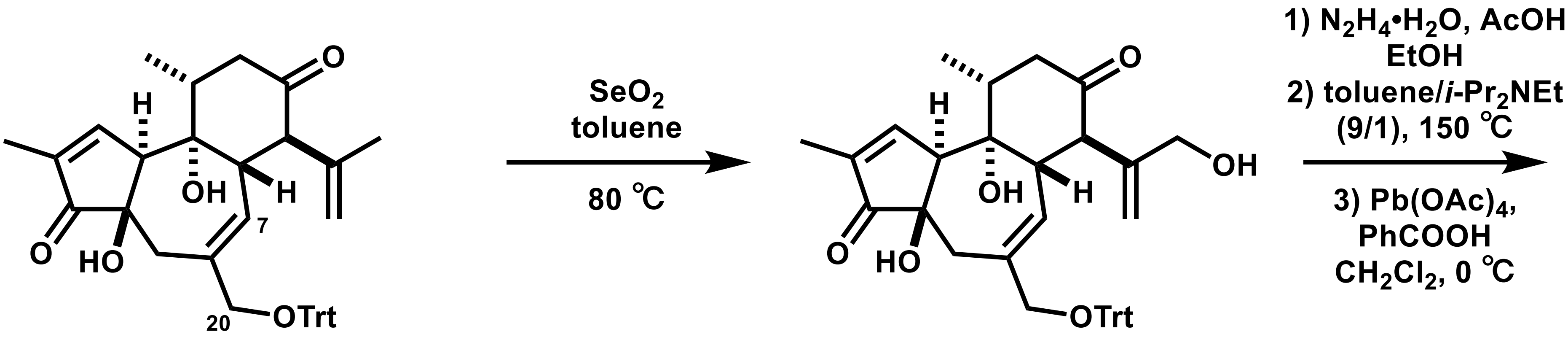


Yield is not mentioned, and "The usual analysis of the product confirms that the desired product XX is present" for all reactions

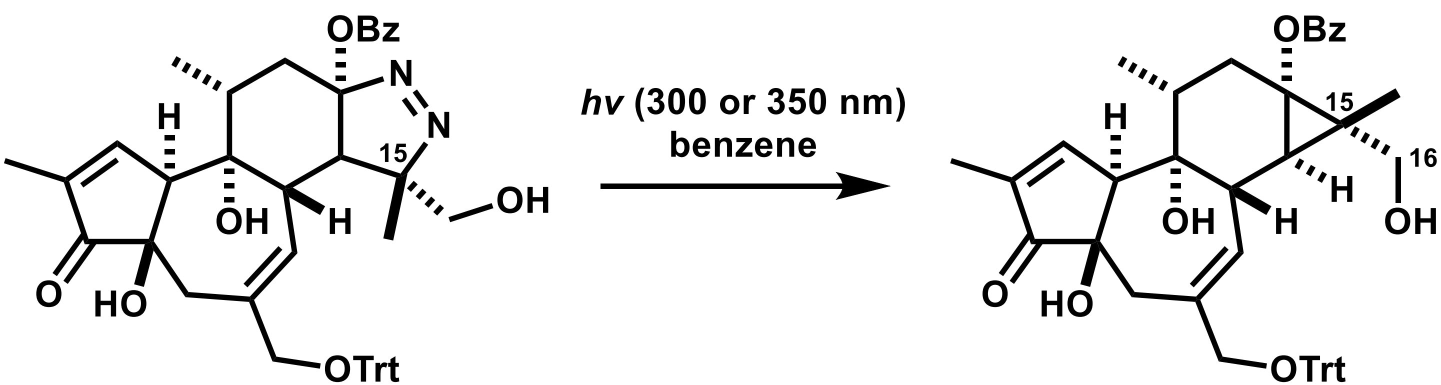
1) Wender, P. A., et al., US 2009/0187046 A1.

Synthesis of C16-Oxy Tigliane

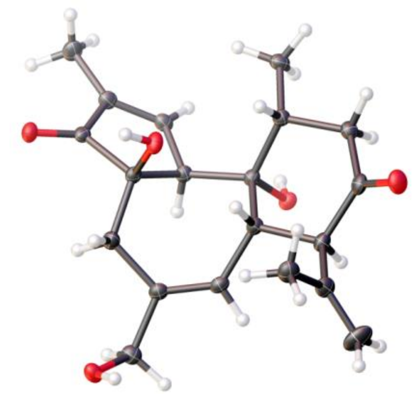
Synthesis of C16-oxy tigliane (<u>PATENT</u>)



protected crotophorbolone



C16-oxy tigliane



X-ray of crotophorbolone

Diastereoselectivity at C15 position is not mentioned
Yield is not mentioned, and "The usual analysis of the product confirms that the desired product XX is present" for all reactions

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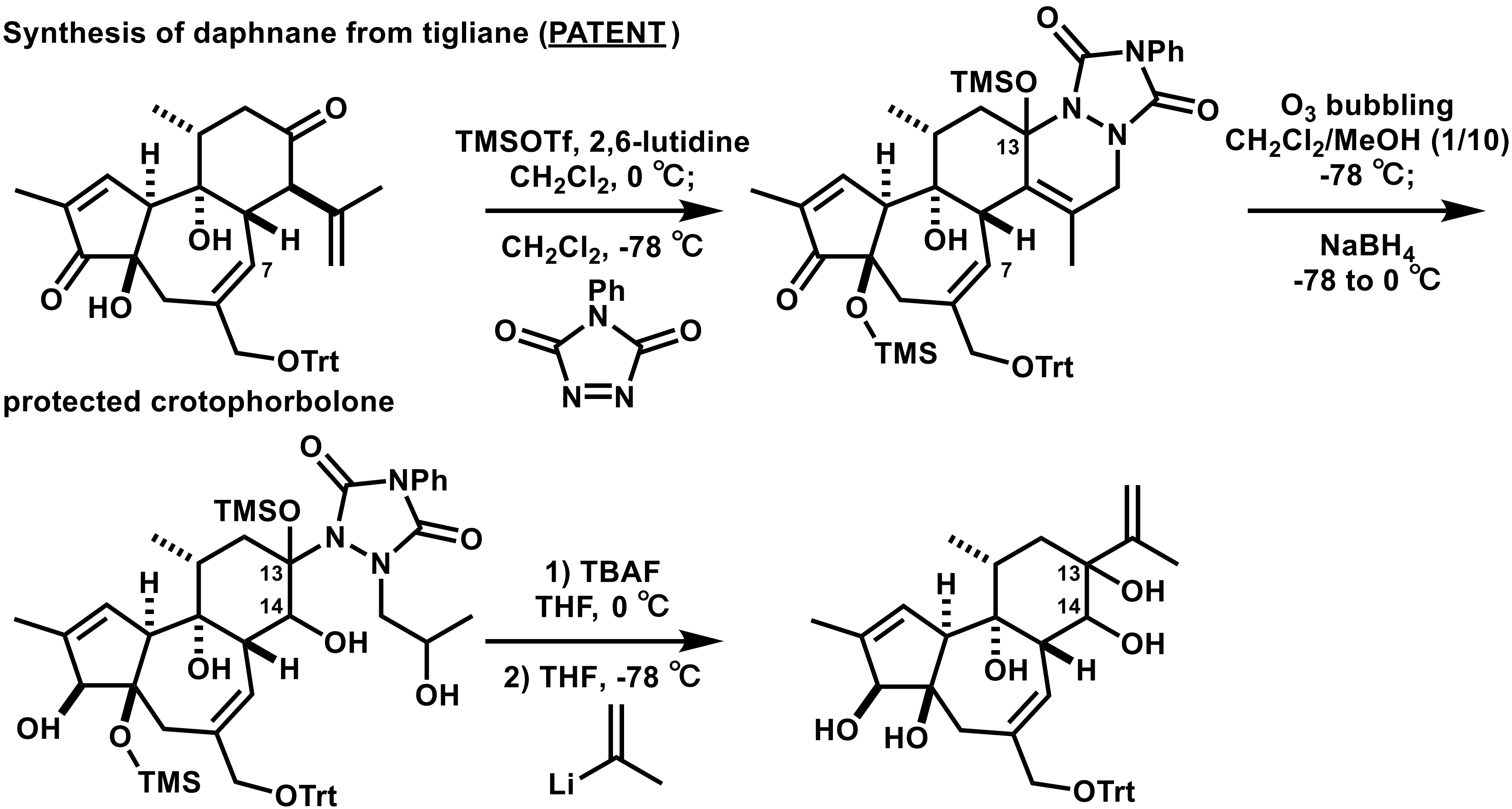
1) Wender, P. A., et al., US 2009/0187046 A1.

Synthesis of Daphnane from Tigliane 1

Synthesis of daphnane from tigliane (PATENT)



protected crotophorbolone

daphnane

Diastereoselectivity at C13 and C14 position is not mentioned
Yield is not mentioned, and "The usual analysis of the product confirms that the desired product XX is present" for all reactions

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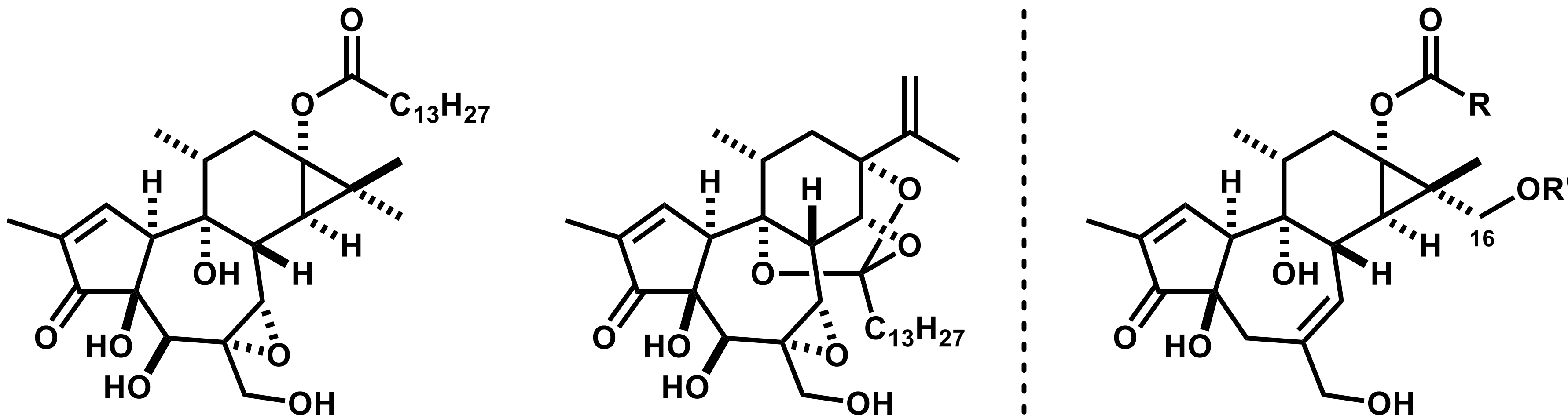
1) Wender, P. A., et al., US 2009/0187046 A1.

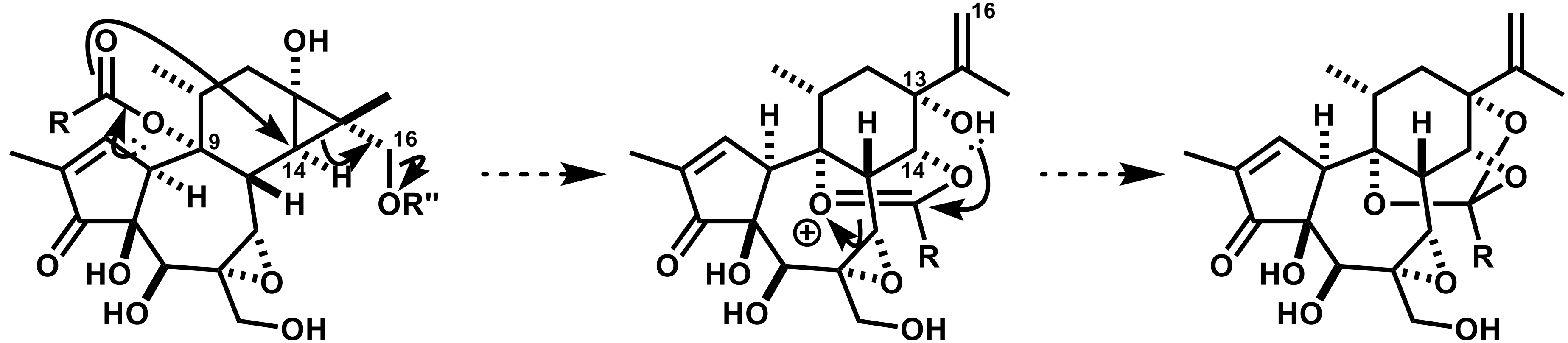
Biomimetic Synthesis of Daphnane 1

Isolaiton of tigliane and daphnane



isolated from a single plant species | **other species**

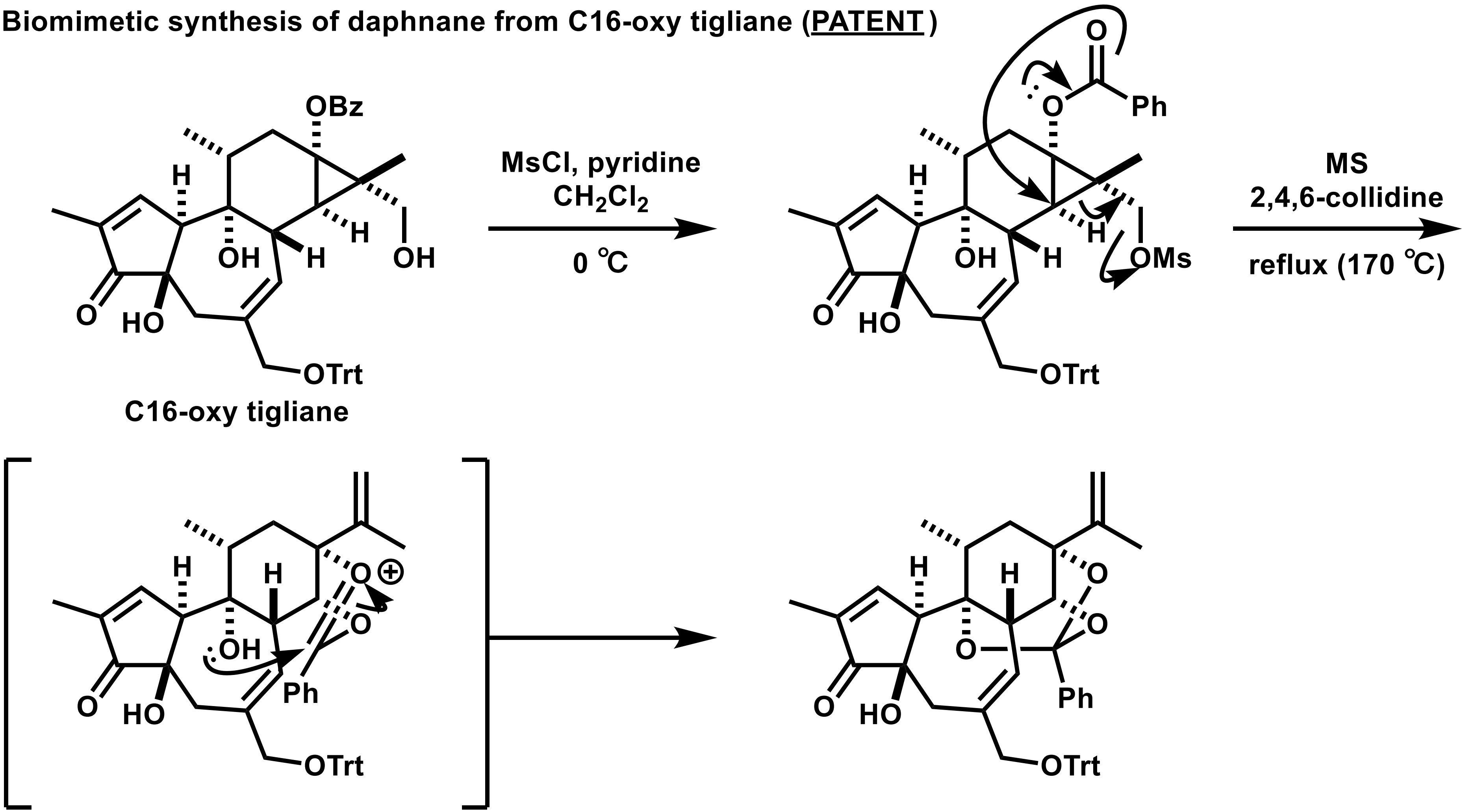
Suggested biosynthetic daphnane fragmentation



1) Magar, S. S.; Desai, R. C.; Fuchs, P. L., *J. Org. Chem.* **1992**, *57*, 5360.
Zayed, S.; Hafez, A.; Adolf, W.; Hecker, E., *Experientia* **1977**, *33*,1554.

Biomimetic Synthesis of Daphnane 2

Biomimetic synthesis of daphnane from C16-oxy tigliane (<u>PATENT</u>)



Yield is not mentioned, and "The usual analysis of the product confirms that the desired product XX is present" for all reactions

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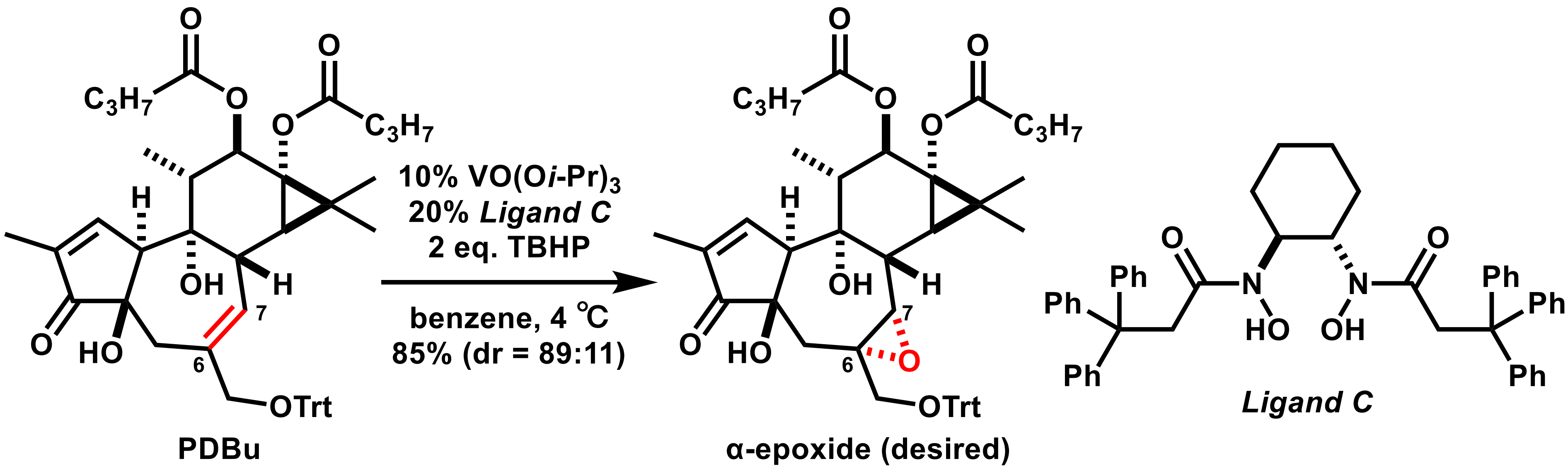
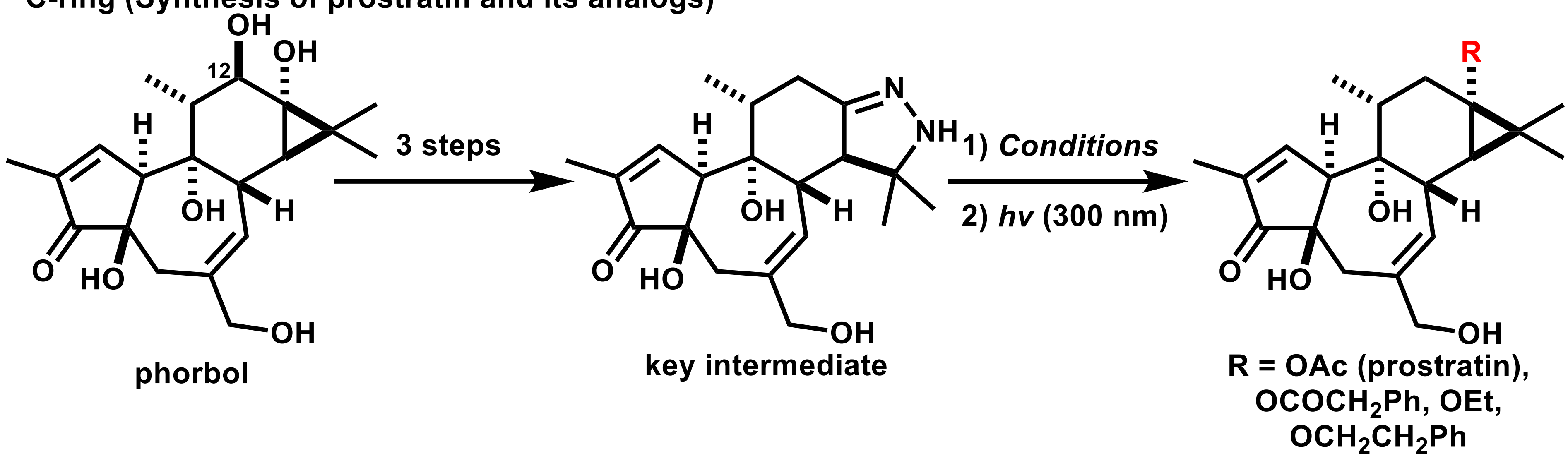
1) Wender, P. A., et al., US 2009/0187046 A1.

Summary 1 (Results)

B-ring (α-epoxidation of tigliane skeltone)

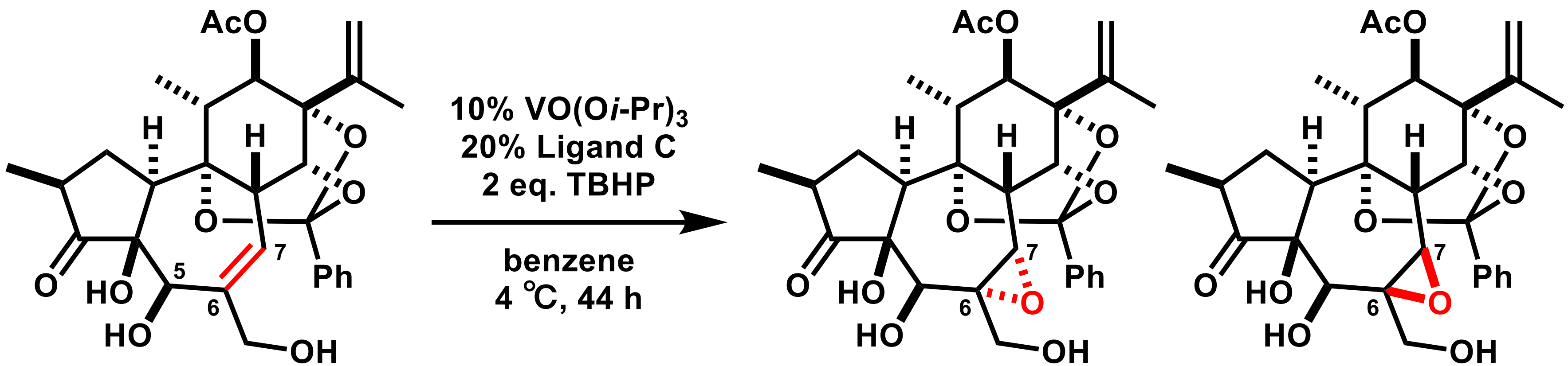


C-ring (Synthesis of prostratin and its analogs)



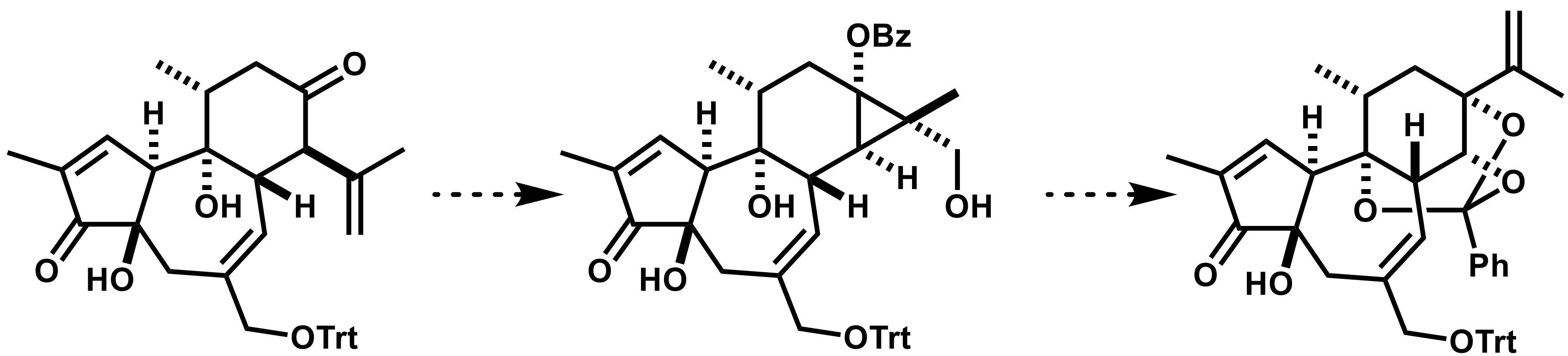
Summary 2 (Remaining Tasks)

B-ring (α-epoxidation of daphnane skeltone)



des-epoxy-yuanhuapin | yuanhuapin **not obtained** | C6,C7-*epi*-yuanhuapin 81%

C-ring (Synthesis of C16-oxy tigliane and fragmentation to daphnane)



Protected crotophorbolone | 16-oxy tigliane | daphnane